REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

Claims 1, 2, 6-9, 13-14, 16-20, and 22-29 are pending. Claims 1, 9, 13, 14, and 16 have been amended. Claim 15 has been canceled. Claims 22-29 have been added. Claim 21 was added in the Amendment filed April 24, 2003, and not entered per the Advisory Action dated May 19, 2003. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claim 1 has been amended to clarify that the aminoalkylmethacrylate copolymer is (a) cationic, and (b) composed of dimethylaminoethyl- and neutral methacrylates, *i.e.*, methyl and butyl methacrylates. See the last paragraph of page 8 for support.

Claim 9 has been amended to qualify the type of "mucosa" through which the claimed preparation is administered. See page 11, lines 27-29 for support.

Claim 13 has been amended to reflect that the ratio of the cationic aminoalkylmethacrylate copolymer to high molecular weight drug is less than 2:1. This amendment is fully supported by the application. See, for instance, Examples 3, 8, 9, 10, and 20, where the ratio is 1:1; Examples 6 and 12, where the ratio is 1.5:1; and Example 25 where the ratio is 1.875:1.

Claim 14 has been amended solely for grammatical reasons to further qualify that ratio, *i.e.*, to qualify the percentage of copolymer in the claimed preparation to be "0.1 to 90% (w/w)" of the powdered preparation. See page 9, lines 11-14 for support.

Claims 22, 23, 27, and 28 have been added to qualify the cationic aminoalkylmethacrylate copolymer by its tradename as "Eudragit® E" and, more specifically, Eudragit® E100. See the last paragraph of page 8 for support.

New claim 26 is directed to a method for enhancing the absorption of a high molecular weight medicine through a mucosal membrane. See pages 11-13 of the specification for support.

At page 2, the specification states that administering a drug larger than 1000 MW was extremely difficult, by means of conventional delivery strategies, and the present invention addresses this problem. Accordingly, new claim 30 qualifies the recited medicine by reference to a molecular weight greater than 1000.

II. Summary of the Office Action

Due to the extensive nature of the Office Action, Applicants summarize the Examiner's rejections below:

(i) The Declaration of Hideaki Nomura references an "insert*," which is missing.

(ii) Claims 1, 7, 9, 13, 15, and 19-20 are rejected under 35 U.S.C. § 102(e) as anticipated by Chen *et al.* (U.S. Patent No. 5,889,051).

(iii) Claims 1, 7, 9, 13, 15, and 19-20 are rejected under 35 U.S.C. § 103(a) as unpatentable over Cumming *et al.* (U.S. Patent No. 6,153,220).

(iv) Claims 1-2, 6-9, 13-17, and 18-20 are rejected under 35 U.S.C. § 103(a) as unpatentable over Norling *et al.* (U.S. Patent No. 5,958,458).

(v) Claim 8 is rejected under 35 U.S.C. § 103(a) as unpatentable over Norling *et al.* (U.S. Patent No. 5,958,458) in view of JP 406065090.

(vi) Claim 18 is rejected under 35 U.S.C. § 103(a) as unpatentable Norling *et al.* (U.S. Patent No. 5,958,458) in view of Stanton *et al.* (U.S. Patent No. 5,807,552).

III. Applicants' Reply to the Office Action

(i) Missing "insert" from Declaration of Hideaki Nomura

The Examiner notes that an "insert" comment in point 11 of Dr. Nomura's Rule 132 declaration, reproduced below, which was filed with Applicants' Preliminary Amendment on June 24, 2003, "was not provided to analyze the claimed data":

> *"11. I conducted the experiments related in Examples [insert*] of the present application, as well as those related in Experiments 1 and 2, which are appended to this Declaration."*

The "[insert*]" note should have simply referred to "Examples 3, 7, 8, 9, and 11 of the present specification," which relate to the superior properties of Eudragit® E100. The "[insert*]" note does not refer to the submission of new data to the patent office.

"Experiments 1 and 2," which are also referred to in point 11 of the declaration, have already been presented to the Examiner in Applicants' paper of April 24, 2003, but apparently were not appended to the Declaration. Applicants have attached, therefore, another copy of Experiments 1 and 2 for the Examiner's review. The undersigned communicated all of this information to Examiner Gollamudi on October 22, 2003, who agreed to this course of action.

(ii) **Chen *et al.* (U.S. Patent No. 5,889,051) not only fails to teach each element of claims 1, 7, 9, 13, 15, and 19-20, respectively, but also teaches away from the claimed invention**

The Examiner alleges that "Chen et al disclose a solid drug dispersion of prostaglandin and instant polymer (Eudragit® RS) in instant amounts." Thus interpreted, the Chen patent is deemed to anticipate claims 1, 7, 9, 13, 15, and 19-20 under Section 102(e). Office Action at page 3.

In fact, Chen *et al.* teaches a stable, solid dispersion of the prostaglandin drug, Misoprostol, which has a *low* molecular weight of 382.5 (col. 2, lines 10-11) and which is formulated with an *ammonio* methacrylate copolymer, such as Eudragit® RS, Eudragit® RL, Eudragit® S, and Eudragit® L (col. 1, line 67-col. 2, line 2; col. 2, lines 17-20 and lines 60-65). Thus, Chen *et al.* says nothing of a cationic aminoalkylmethacrylate copolymer comprised of *dimethylaminoethyl* methacrylate and methyl- and butyl-methacrylates, in combination with a *high* molecular weight medicine.

Ammonio methacrylates are chemically distinct from a dimethylaminoethyl methacrylate copolymer, as presently recited. Moreover, ammonio methacrylates confer "sustained release" to a co-formulated drug. Not surprisingly, therefore, Chen's drug formulation is of a sustained-release therapeutic (see col. 2, line 6). By contrast, the presently recited copolymer does not confer sustained release on a co-formulated drug. See the "Rohm Pharma Polymers" product literature appended to this paper. Accordingly, Chen *et al.* does not anticipate the present claims, and Applicants request that the Examiner withdraw this rejection.

(iii) **Cumming *et al.* (U.S. Patent No. 6,153,220) does not suggest admixing Eudragit® E100 with a high molecular weight medicine so as to improve the absorption of the medicine through a mucosal membrane as recited in claims 1, 7, 9, 13, 15, and 19-20**

The Examiner states that Cumming *et al.* teaches a "taste-masked" formulation that contains a cationic copolymer, specifically Eudragit® E100, and a drug in powder form. According to the Examiner, "it is deemed obvious to one of ordinary skill in the art ... to look to the guidance provided by Cumming and utilize the instant drugs in the composition. One would be motivated to do so since Cumming teaches the suitability of proteins, peptides, and hormones as the active ingredient." Office Action at page 4.

In the present specification, Applicants detail the problems faced heretofore in attempts to administer a high molecular weight drug through a mucosal membrane. With conventional technology, "effective absorption" of medicines that are greater than 1000 MW is "difficult to achieve without some contrivance ... Thus, it has been difficult to achieve therapeutic effect by administration of high molecular weight medicines through nasal mucosa" (page 2, lines 7-13 of the specification). For example, while surfactants, bile acid salts, and cyclodextrin had been used in the art as absorption promoting agents, they were deemed to be harmful to nasal mucosa. Similarly, formulations comprising absorption agents such as albumin, dextran or sodium hyaluronate lack industrial applicability and, more importantly, do not effectively improve the absorption of high molecular weight drugs through mucosa (page 3, lines 2-7).

Cumming addresses none of these problems and says nothing that implicates Applicants' solution, namely, a methacrylate-based preparation for improving transmission of a high molecular weight drug through mucosa, as recited in claim 1. Indeed, the exemplary drugs of Cumming, Nizatidine and Roxadine, have a *low* molecular weight of about 350.

The methacrylate in Cumming's composition disguises the taste of "drugs having foul organoleptic properties" (col. 2, lines 20-23). Accordingly, the composition comprises a cationic methacrylate copolymer "in amounts *significantly greater* than the amount of drug" to avoid "the unpleasant possibility of a taste-masking coating being breached by mastication or insufficient amounts of taste masker being present to provide adequate elimination of the unpleasant organoleptic properties of the drug (emphasis added; col. 1, line 67 to col. 2, line 2).

Thus, the ratio of cationic copolymer to a "drug having poor organoleptic properties" is "greater than 2 to 1, preferably 4 to 1, most preferably 6 to 1 when compared weight to weight" (col.

2, lines 10-16). To the contrary, present claims 13, 14, and 24 require the ratio of cationic copolymer to high molecular weight medicine of claim 1 to be less than 2 to 1 and are, therefore, separately patentable over Cumming *et al.*

There is nothing in Cumming to have suggested that a composition comprising less methacrylate copolymer than drug would enhance the transmission of a high molecular weight drug across a mucosal membrane. Rather, the skilled artisan would have expected such a composition actually to *increase* "the unpleasant possibility" that the taste of the drug would be discernable. For this reason, if presented with a high molecular drug, the skilled artisan would have been motivated to add even more methacrylate copolymer, so as to ensure that the taste of the larger drug is properly disguised. To that end, Cumming does not speak to all drugs but only to those "having poor organoleptic properties." By the same token, there would be no need to incorporate a cationic methacrylate copolymer with a drug that has no foul organoleptic properties.

Cumming therefore does not suggest the powdered preparation of claim 1, nor the required polymer to medicine ratio recited in claims 13, 14, and 24. Accordingly, the present claims are non-obvious over Cumming *et al.* and Applicants, therefore, request that the Examiner withdraw this rejection.

(iv) Claims 1-2, 6-9, 13-17, and 18-20 are not rendered obvious by Norling *et al.* (U.S. Patent No. 5,958,458) because the preparation of claim 1 consists essentially of a high molecular weight medicine and methacrylate copolymer

The Examiner rejected claims 1-2, 6-9, 13-17, and 18-20 as obvious over Norling *et al.* According to the Examiner, the Norling reference discloses "a particulate formulation in the form of coated cores ... which additionally contain a coating such as ... Eudragit® E." Office Action at page 4. The Examiner concludes that, while Norling does not "exemplify instant drugs," it would have been obvious to modify Norling because "Norling teaches insulin, calcitonin, GCSF [*sic*: "CSF"]."

Amended claim 1 employs a transitional phrase, "consisting essentially of," that accommodates only components "that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). Because Norling's "inert carrier" material and unit "cores" would materially affect the characteristics of the presently recited preparation, claim 1 and its dependents cannot be rendered obvious by Norling *et al.*

According to Norling, an inert carrier, such as calcium carbonate or calcium silicate, confers a structural rigidity to the spherical cores onto which a desired drug is coated. Indeed, Norling observed that cores that lack an inert carrier were "hollow" and, therefore, unable to structurally withstand the drug-coating process. For that reason, Norling considered it "almost impossible" to coat a hollow core unless it had been filled with an inert carrier (col. 3, lines 51-64). Thus, Norling's inert carrier provides "such a mechanical strength that the cores are sufficiently robust to substantially remain intact after having been subjected to coating" (col.2, lines 33-39).

It necessarily follows that a "robust" complex of a high MW medicine, a unit core, and an inert carrier, which prevents disintegration of the complex, would reduce the ability of the recited methacrylates to transport that complex effectively across a mucosal membrane, in the manner disclosed by Applicants. Thus, the skilled artisan would not have thought that an inert carrier/core complex would promote the pernasal absorption of a high MW drug.

Applicants' unexpected discovery is that the claimed composition is able to increase the rate at which high molecular weight medicines are absorbed through a mucosal membrane, beyond what is possible with various other drug formulations. See Examples 3, 7, 8, 9, and 11 of the present specification and appended Experiments 1 and 2. At least for these reasons, Norling does not render the present claims as obvious. Accordingly, Applicants respectfully request that the Examiner withdraw this rejection.

(v) **Neither the combination of Norling *et al.* (U.S. Patent No. 5,958,458) and JP 406065090 or Norling *et al.* and Stanton *et al.* (U.S. Patent No. 5,807,552) suggest a G-CSF or hapten-conjugated methacrylate composition that does not have an inert carrier core, as presently recited**

The Examiner rejects claim 8 as obvious in light of Norling in view of JP 406065090 ("JP"), because it allegedly would have been obvious to utilize the G-CSF of JP in Norling's coated cores, since Norling "teach the suitability of CSF in the formulation."

For the reasons set forth in subsection (iv) above, Norling does not render the present claims as obvious. At most, after having read JP and Norling, the skilled artisan would have been motivated to admix a core, an inert carrier, G-CSF, and an "acrylate polymer" film coating. The skilled artisan would not have been prompted to omit Norling's inert carrier and simply coat JP's G-CSF with an acrylate polymer. Furthermore, the skilled artisan would not have expected that by modifying Norling in such fashion that they would be able to increase the absorbance of G-CSF across a mucosal membrane by 100-fold, as Applicants' unexpected results demonstrate.

For similar reasons, the skilled artisan would not have been motivated to combine the teachings of Norling and Stanton (U.S. patent No. 5,807,552) to utilize a hapten conjugated protein in Norling's pharmaceutical composition. At most, the skilled artisan would have been motivated to add a hapten conjugated protein to the outer layer of an inert carrier core and to coat that core with an acrylate polymer film. There is nothing in Stanton to suggest a composition that lacks an "inert-core," but which comprises a hapten-conjugated protein and the recited methacrylates.

Accordingly, neither the combination of Norling and JP, nor the combination of Norling and Stanton, renders the claimed invention obvious. Accordingly, Applicants respectfully request that the Examiner withdraw these rejections.

Applicants believe that the present application now is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 4 December 2003 By S. A. Bent

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